VALUE IN HEALTH 15 (2012) 255–260

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Cost-Effectiveness of Adjuvant FOLFOX Therapy for Stage III Colon Cancer in Japan Based on the MOSAIC Trial

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A B S T R A C T

Objective: To evaluate the cost-effectiveness of adjuvant FOLFOX therapy versus 5-fluorouracil/leucovorin (FU/LV) for patients with stage III colorectal cancer. **Methods:** We performed the cost-effectiveness of FOLFOX compared with standard FU/LV treatment by the retrospective analysis of patient-level data from the randomized controlled Multicenter International Study of Oxaliplatin, 5-Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial. Predicted mean time spent in each disease state was calculated by our statistical model, which takes into account the cure rate and treats death from causes other than colon cancer as a competing risk. We performed this analysis from the perspective of the health-care payer. Using a time horizon of 30 years, both cost and effectiveness were discounted by 3% per year. **Results:** Estimated cure rates for colon cancer were 0.715 (FOLFOX) and 0.622 (FU/LV). Estimated medical costs of FOLFOX were JPY 3.1 million (USD 34,000) compared with JPY 1.9 million (USD 22,000) of FU/LV. The mean estimated quality-adjusted life-year was 9.83 with FOLFOX and 9.07 with that of FU/LV. The incremental cost-effectiveness ratio of FOLFOX was JPY 1.5 million (USD 17,000) per quality-adjusted life-year compared with FU/LV, which was supported by sensitivity analysis. Even if we assume that Japanese outcomes were better than those reported by the MOSAIC trial, which would reduce the difference between cure rates for each treatment to 5%, the incremental cost-effectiveness ratio remained below 5.0 million (USD 56,000) per quality-adjusted life-year. **Conclusions:** Adjuvant FOLFOX is a cost-effective treatment for stage III colon cancer in Japan compared with FU/LV therapy. Even when parameters were changed to reflect smaller improvements with FOLFOX, the conclusion is the same.

Keywords: adjuvant drug therapy, colon cancer, cost-effectiveness, FOLFOX regimen, oxaliplatin.

Introduction

After lung and stomach cancer, colon cancer is the third leading cause of death from malignant neoplasm in Japan. Age-adjusted mortality for colon cancer is 12.5 deaths per 100,000 for men and 8.6 deaths per 100,000 for women. Although this rate has decreased from its peak around 2000, more than 28,000 people died from colon cancer in 2009 [1]. Thus, colorectal cancer remains an important public health issue.

Surgery and radiation therapy are standard treatments for early-stage colon cancer; however, to reduce the risk of recurrence and extend survival, chemotherapy may be administered as adjuvant therapy to inhibit residual micrometastases in lymph nodes and elsewhere in the body [2]. A pooled analysis of randomized controlled trials (RCTs) showed that combined 5-fluorouracil/leucovorin (FU/LV) treatment reduced recurrence by 35% and death by 22% after potentially curative resection of colon cancer compared with no treatment [3]. FU/LV was shown to be superior to other regimens, such as the lomustine, vincristine, and 5-FU regimen [4] and the FU and levamisole regimen [5]; thus, FU/LV became the standard adjuvant chemotherapy regimen for colon cancer. FU/LV adjuvant therapy is also the standard care in Japan.

The FOLFOX regimen for metastatic colorectal cancer consists of oxaliplatin, a platinum-based anticancer drug, combined with FU/LV. RCTs have demonstrated that the FOLFOX regimen prolongs progression-free survival and overall survival (OS) compared with FU/LV for patients with metastatic disease [6]. In addition, FOLFOX is superior to FU/LV as an adjuvant therapy [7,8]. The Multicenter International Study of Oxaliplatin, 5-Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial reported that FOLFOX improves the adjuvant treatment of colon cancer [7]. In the MOSAIC trial, the 3-year disease-free survival (DFS) rate was 78.2% for patients receiving FOLFOX and 72.9% for those receiving FU/LV (hazard ratio for recurrence 0.77; $P = 0.002$). At 5 years, the DFS was 73.3% in the FOLFOX group and 67.4% in the FU/LV group. In patients with stage III cancer, the 6-year OS was 72.9% in the FOLFOX group and 68.7% in the FU/LV group (hazard ratio 0.80; $P = 0.023$) [9].

Some studies [10–12] have suggested that FOLFOX is a cost-effective treatment compared with FU/LV; however, some Japanese oncologists believe that the recurrence rate for colorectal cancer is lower in Japan than in European and North American countries. They therefore tend to be reluctant to use adjuvant FOLFOX therapy because they believe that Japanese patients will not benefit from adjuvant FOLFOX as much as patients who

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1098-3015/$36.00 – see front matter

doi:10.1016/j.jval.2011.10.006

participated in the MOSAIC trial. This is complicated by the issue of heterogeneity of clinical outcomes or how to extrapolate results from a large multinational RCT to cost-effectiveness analyses in each country. If the results of a multinational RCT are applied to economic evaluations, then heterogeneity of clinical outcomes should be taken into account. The present study focused on this theme. To reflect heterogeneity of baseline outcomes and clinical benefit from FOLFOX and to extrapolate the survival curve more appropriately, we used an elaborated statistical model that can account for cure rate; few others have taken advantage of this model. With this statistical model, we performed an economic evaluation of adjuvant FOLFOX therapy for patients with stage III colorectal cancer based on patient-level data from the MOSAIC trial.

Methods

Chemotherapy regimens

We retrospectively analyzed patient-level data from the multinational randomized controlled MOSAIC trial. We used the data of patient characteristics, DFS, and OS at 3 years, as well as dose of oxaliplatin.

In the MOSAIC trial, stage II and stage III patients were randomized to one of two treatment groups: FOLFOX, which consisted of 12 cycles of oxaliplatin (85 mg/m^2 intravenous infusion) on day 1 of the 2-week cycle, LV (200 mg/m^2 intravenous infusion) on days 1 and 2, and 5-FU (400 mg/m^2 bolus intravenous injection followed by 600 mg/m^2 continuous infusion for 22 hours) on days 1 and 2, or FU/LV, which was the same regimen as FOLFOX treatment, but without oxaliplatin.

The MOSAIC trial enrolled patients with stage II and stage III colon cancer; however, we assumed that FOLFOX therapy would be used primarily for patients with stage III cancer in Japan. Therefore, we limited the target population to the stage III colon cancer intent-to-treat subpopulation, and patients who did not receive even a single dose of the predetermined chemotherapy protocol were excluded. The intent-to-treat subpopulation (stage III) from the MOSAIC trial used in our analysis was FOLFOX (n = 672) and FU/LV (n = 675). Demographic characteristics of our targeted population were the same as those reported by the MOSAIC trial; median age was 60 years, and the ratio of male and female was 1:1.

Framework of economic analysis

We performed a cost-effectiveness analysis of FOLFOX adjuvant chemotherapy compared with FU/LV for the treatment of stage III colon cancer. Our analysis was based on recommendations of the Panel on Cost-Effectiveness in Health and Medicine [13]. Quality-adjusted life-years (QALYs) were used to calculate the incremental cost-effectiveness ratio (ICER).

We considered three conditions: DFS, metastatic recurrence, and death. The mean time spent in each state was estimated by methods described in the "Statistical Analysis" section. Utility scores were 0.8 (DFS), 0.6 (metastatic recurrence), and 0 (death) based on a Japanese study that measured general population utility scores of colorectal cancer by using time trade-off and standard gamble methods [14].

This cost-effectiveness analysis was performed from the perspective of the health-care payer and included only direct medical costs, not indirect costs (e.g., productivity costs). Using a time horizon of 30 years, both cost and effectiveness were

Table 1 – Breakdown of chemotherapy costs.

	Unit cost (JPY)	Number (per month)		Price (JPY per month)	
		FOLFOX	FU/LV	FOLFOX	FU/LV
Outpatient chemotherapy				45,000	32,000
Granisetron 3 mg	5494	2	0	10,988	0
Dexamethasone 3.3 mg (vial)	195	6	6	1170	1170
Dexamethasone 3.3 mg (tablet)	6	64	0	378	0
Outpatient service fee	700	4	4	2800	2800
IV drip fee	980	4	4	3920	3920
Preparation in sterile environment	500	4	4	2000	2000
Outpatient chemotherapy	5500	4	4	22,000	22,000
Prescription fee	680	2	0	1360	0
Diagnositc imaging				4100	4100
Chest CT scan	6600	1 of 6	1 of 6	1100	1100
Abdominal CT scan	6600	1 of 6	1 of 6	1100	1100
Pelvic CT scan	6600	1 of 6	1 of 6	1100	1100
CT scan diagnostic fee	4500	1 of 6	1 of 6	750	750
Blood test				8700	8700
Blood drawing fee	180	2	2	360	360
Peripheral blood tests fee	210	2	2	420	420
Peripheral blood tests diagnostic fee	1250	1	1	1250	1250
Biochemical tests fee	1230	1	1	1230	1230
Biochemical tests diagnostic fee	1440	1	1	1440	1440
Tumor maker tests fee	4000	1	1	4000	4000
Pharmacy costs				1900	0
Pharmacist's fee	400	2	0	800	0
Dispensing fee	100	2	0	200	0
Management of drug history	300	2	0	600	0
Drug information providing fee	150	2	0	300	0

CT, computed tomography; FU/LV, 5-fluorouracil/leucovorin; JPY, Japanese yen; IV, intravenous.

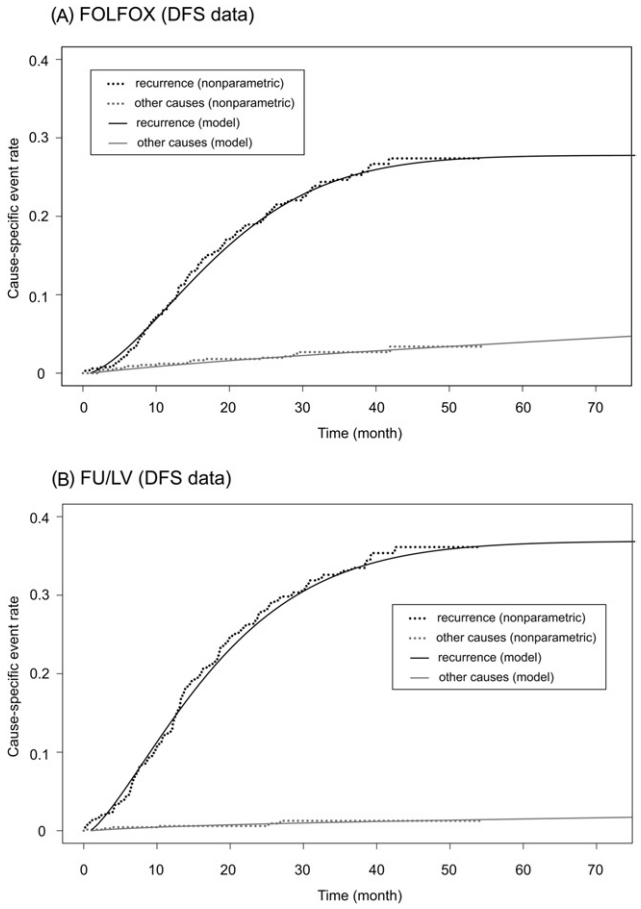

Fig. 1 – Estimated cumulative incidence function curves: (A) FOLFOX and (B) 5-fluorouracil/leucovorin (FU/LV). DFS, disease-free survival.

discounted by 3% per year. Results were subjected to sensitivity analysis.

Medical resource use and costs

All costs are expressed in Japanese yen (JPY) and US dollars (USD) using an exchange rate of USD 1 = JPY 90 (as of June 2010). Individual costs of oxaliplatin treatment until completion or termination of treatment, estimated by multiplying patient dose by the price of oxaliplatin, were JPY 70,284 (USD 780) for 100 mg and JPY 38,142 (USD 420) for 50 mg. Because patient-level data were not available for FU/LV consumption, we simply added the cost of FU/LV treatment, JPY 120,000 (USD 1300) per month multiplied by FU dose intensity. As l-LV (isovorin) 100 mg/m^2 is used instead of LV (leucovorin) 200 mg/m^2 in Japan, chemotherapy costs were calculated on the basis of l-LV.

For adjuvant therapy costs, we also added the costs of outpatient chemotherapy (JPY 45,000 [USD 500] per month for FOLFOX and JPY 32,000 [USD 350] per month for FU/LV), diagnostic imaging (JPY 4100 [USD 45] per month), laboratory tests (JPY 8700 [USD 97] per month), and pharmacy (JPY 1900 [USD 21] per month for FOLFOX) (Table 1) [15]. After the completion of adjuvant chemotherapy, disease-monitoring costs (JPY 7000 [USD 80]) were also included for 5 years, following the Japanese guidelines for colorectal cancer.

Costs of metastasis were calculated on basis of the following scenarios [15,16]: 1) JPY 2.0 million to JPY 2.5 million (USD 22,000–USD 28,000) per year for FOLFOX plus bevacizumab as first-line chemotherapy and FOLFIRI as second-line therapy; 2) JPY 2.5 million to JPY 3.5 million (USD 28,000–USD 39,000) per year for FOLFOX plus bevacizumab as first-line chemotherapy, FORFIRI as second-line chemotherapy, and cetuximab as third-line chemotherapy; or 3) JPY 1.0 million to JPY 1.5 million (USD 11,000–USD 17,000) for FOLFOX as first-line chemotherapy and FORFIRI as second-line chemotherapy without monoclonal antibody therapy. We used JPY 2.0 million per year for our base-case analysis because bevacizumab or cetuximab is administered to many patients with metastatic colorectal cancer. This cost was subject to sensitivity analysis. Adverse event (AE) costs were not included in the base-case analysis, because costs were unclear and the difference in costs was not expected to be large. AE costs were also subject to sensitivity analysis.

Costs were calculated for 2010 according to the social insurance reimbursement schedule [15] and drug tariff [16] of the fee-for-service system in Japan, which excludes inpatient treatment at large hospitals. Censored data were considered to calculate mean cost per patient, according to the method of Lin et al. [17]. Confidence intervals for mean costs were obtained by the bootstrap method.

Statistical analysis

Although some patients with colon cancer experience metastatic recurrence, some cancers are completely cured without recurrence. Therefore, a simple parametric survival analysis cannot adequately predict patient prognosis. We applied the Weibull curve (with cure probability) to cumulative incidence function for cancer in the following way:

$$S(t) = p + (1-p)\exp\left[-(\beta t)^{\alpha}\right]$$

where p is the cure rate of colon cancer [18]. To model the OS curve, we used the cure rate previously estimated by DFS data. Deaths from causes other than colon cancer were considered a competing risk. After 60 months, the hazard of death from other causes was thought to be equal to that of the general population of the same age. Appendix A found at doi:10.1016/j.jval.2011.10.006 provides a detailed description of the statistical method to estimate survival curves.

Using the estimated survival curve, mean progression-free survival and OS were calculated by taking the area under each survival curve. We calculated the QALY gain of group i with the following equation:

$$D_i U_{\mathrm{DFS},i} + \left(O_i - D_i\right) U_{\mathrm{DP}}$$

where D_i is the mean DFS for group i, O_i is the mean OS of group i, $u_{\mathrm{DFS},i}$ is the utility score of DFS (group i), and U_{DP} is the utility score of disease progression.

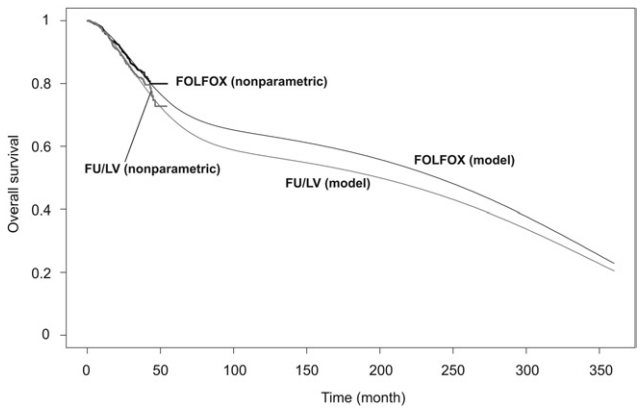

Fig. 2 – Estimated overall survival curves. FU/LV, 5-fluorouracil/leucovorin.

Table 2 – Results of cost-effectiveness analysis.

	Cost	Incremental cost (JPY 10,000)	Effectiveness (QALY)	Incremental effectiveness (QALY)
FU/LV	194	–	9.07	–
FOLFOX	307	113	9.83	0.76
95% CI		34 to 174		−0.08 to 1.62
			ICER (JPY 10,000 per QALY)	
			149	

CI, confidence interval; FU/LV, 5-fluorouracil/leucovorin; JPY, Japanese yen; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Because some Japanese oncologists believe that the recurrence rate of colorectal cancer in Japan is lower than that of European and North American countries, we performed sensitivity analysis on the estimated cure rate. We increased the cure rate and reduced the treatment difference compared with that reported by the MOSAIC trial. The following four parameters were also subject to sensitivity analysis: 1) cost of metastasis, 2) time horizon, 3) cost of AE, and 4) discount rate. Uncertainty of the ICER was estimated by the bootstrap method (in which bootstrap resampling was repeated 10,000 times).

Results

Survival curve estimation

Estimated DFS and OS curves are shown in Figures 1 and 2. The estimated cure rate of colon cancer was 0.715 with FOLFOX treatment and 0.622 with FU/LV treatment. The estimated 5-year DFS was 0.684 with FOLFOX and 0.619 with FU/LV, and the estimated 6-year OS was 0.688 with FOLFOX and 0.640 with FU/LV. Estimated mean OS was 12.4 years (3% discount) and 17.2 years (0% discount) with FOLFOX and 11.4 years (3% discount) and 15.8 years (0% discount) with FU/LV.

Base-case analysis

Results of base-case cost-effectiveness analysis are shown in Table 2. Expected medical costs of FOLFOX therapy were estimated at JPY 3.1 million (USD 34,000), which increases medical costs by JPY 1.1 million (USD 13,000) compared with FU/LV therapy (JPY 1.9 million [USD 22,000]). The mean estimated QALY was 9.83 with FOLFOX and 9.07 with FU/LV; the difference was 0.76 QALY. The ICER with FOLFOX was JPY 1.5 million (USD 17,000) per QALY compared with FU/LV.

Results of sensitivity analysis

We first changed the parameter of cure rate. Although we estimated a cure rate difference of 9.3%, we lowered this difference to 7.5% and 5%. The 7.5% difference was almost equal to the 5-year DFS difference reported by the MOSAIC trial. When we assumed that Japanese outcomes were better than those of European and North American countries, the cure rate difference exerted more influence on the ICER than did the absolute cure rate. Nevertheless, in the most conservative setting, the ICER of FOLFOX was less than JPY 5.0 million (USD 56,000) per QALY (Table 3).

The ICER increased with shorter time horizons and lower costs of metastasis (Table 4). With a 10-year time horizon and metastatic cost of JPY 1.0 million per year, the ICER increased to JPY 4.4 million (USD 49,000) per QALY. Increasing the discount rate from 0% to 6% increased the ICER from JPY 1.1 million (USD 12,000) to JPY 2.3 million (USD 26,000) per QALY. With an additive mean AE cost of JPY 50,000 per patient, the ICER was JPY 1.7 million (USD 19,000), but at an additive mean AE cost of JPY 200,000 per person, the ICER increased to JPY 1.9 million (USD 21,000) per QALY. Other parameters (such as utility scores and drug costs) had small influence on the results.

The relationship between incremental cost and incremental effectiveness is shown in Figure 3. The cost-effectiveness acceptability curve is shown in Figure 4. The probability that FOLOFX is cost-effective was approximately 90% when the willingness to pay for one QALY was JPY 5.0 million (USD 56,000).

Discussion

Our cost-effectiveness analysis showed that the ICER of FOLFOX therapy was 1.5 million (USD 17,000) per QALY. This result was supported by sensitivity analysis. Even if we assume that Japanese outcomes are better than those reported by the MOSAIC trial and when the difference between colon cancer cure rates was decreased to 5%, the ICER remained below 5.0 million (USD 56,000) per QALY. AE costs, which were not included in the base-case analysis, did not strongly influence the ICER of FOLFOX. As expected, when the time horizon was shorter (to exclude the uncertainty of the distant future), the ICER increased. The ICER was estimated at JPY 3.4 million (USD 38,000) to JPY 4.4 million (USD 49,000) per QALY depending on metastatic costs. Although this analysis did not include indirect costs, we would surmise that the

Table 3 – Results of sensitivity analysis: cure rate of colon cancer.

	More conservative (treatment difference = 7.5%)			Most conservative (treatment difference = 5%)		
FOLFOX	75%	80%	82.5%	75%	80%	82.5%
FU/LV	67.5%	72.5%	75%	70%	75%	77.5%
ICER	222	231	236	428	452	465

FU/LV, 5-fluorouracil/leucovorin; ICER, incremental cost-effectiveness ratio.

Table 4 – Results of sensitivity analysis: time horizon and metastatic cost.

Cost of metastasis (JPY 10,000 per y)	Time horizon (y)			
	10	15	20	30
100	444	278	216	174
150	409	257	201	161
200	375	236	184	149
250	341	216	169	137

JPY, Japanese yen.

ICER improves because productivity loss is larger in the FU/LV group than in the FOLFOX group.

In Japan, no consensus exists with regard to the threshold of acceptable cost per QALY saved. The National Institute for Health and Clinical Excellence in the United Kingdom uses a threshold range of £20,000 to £30,000 (approximately JPY 2.5 million to JPY 4.5 million) [19], and in the United States, a threshold range of USD 50,000 to USD 100,000 (JPY 4.5 million to JPY 9.0 million) is often used. A Japanese study on willingness to pay for an additional one QALY suggests JPY 5.0 million to JPY 6.0 million is an appropriate threshold [20]. Considering these criteria, the ICER of FOLFOX is thought to be acceptable.

Our parametric statistical model explicitly takes into account the colon cancer cure rate and treats the risk of death by causes other than colon cancer as competing risk. This model can be applied to other cancers. Our estimated survival curves fit the nonparametric curves well. Our analysis is based on data collected at 3 years; however, the 5-year results were published after the present study was initiated. We estimated the 5-year DFS at 0.684 with FOLFOX and 0.619 with FU/LV; the estimated 6-year OS was 0.692 with FOLFOX and 0.638 with FU/LV. The MOSAIC trial reported that the 5-year DFS was 0.664 with FOLFOX and 0.589 with FU/LV, and the estimated 6-year OS was 0.729 with FOLFOX and 0.687 with FU/LV.

Our estimated cure rates were 0.715 (FOLFOX) and 0.622 (FU/LV). According to the Japanese guidelines for colorectal cancer, recurrence is 0.241 (no recurrence: 0.759) in stage IIIA and 0.408 (no recurrence: 0.592) in stage IIIB. The MOSAIC trial included stage IIIA and stage IIIB patients, suggesting that these estimated cure rates are valid.

A Canadian analysis reported that the ICER of FOLFOX was CAD 24,104 (JPY 2.0 million; CAD 1 = JPY 85) per QALY on the basis of the same MOSAIC trial [12]. This analysis was based on a 50-year time horizon and an annual 5% discount rate applied to both outcome and cost. A US cost-effectiveness analysis estimated the ICER at USD 22,800 (JPY 2.1 million) per QALY using a 3% discount rate [11]. These similar ICER values suggest that our analysis is robust. The National Institute for Health and Clinical Excellence in the United Kingdom also recommended first-line FOLFOX therapy for colon cancer in 2006 [21].

There are several limitations of our analysis. First, we were unable to obtain all patient-level data needed to perform economic evaluation. For example, we used utility scores that were aggregated data from other published articles, and data on the consumption of 5-FU and l-LV were not available. Second, resource use data for treatment of AE were not known. Although costs of AEs associated with FOLFOX are higher than those of FU/LV, we cannot include the costs in the base-case analysis. The sensitivity analysis showed that AE costs had little influence on the results; however, this is another limitation of our analysis. Finally, it is possible that Japanese outcomes and resource use of adjuvant therapy do not differ from those of the countries that participated in the MOSAIC trial. In Japan, a phase I/II study was conducted, but the sample size was small. Although we do not necessarily agree with Japanese oncologists who insist that Japanese outcomes are better than those of other countries, it cannot be denied that outcomes of Japanese patients differ from those of patients from other countries. In addition, the Japanese dose of oxaliplatin may be smaller than the dose used in European and North American countries because Japanese patients have a smaller body surface area. Therefore, when FOLFOX regimens are administered in Japan, the expected costs and ICER may be lower than our estimation.

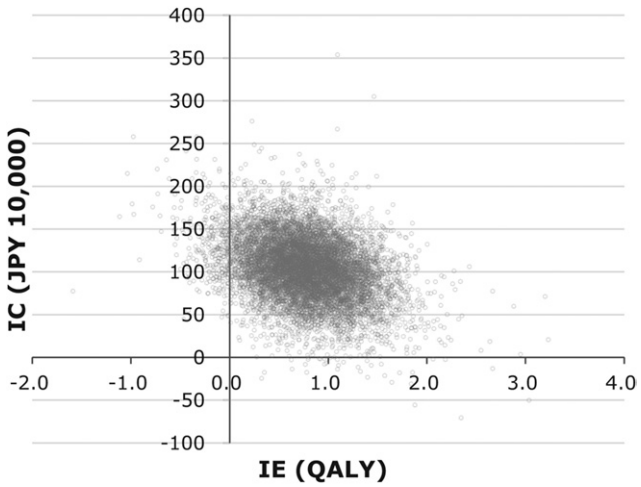

Fig. 3 – Distribution of incremental effectiveness (IE) and incremental cost (IC). JPY, Japanese yen.

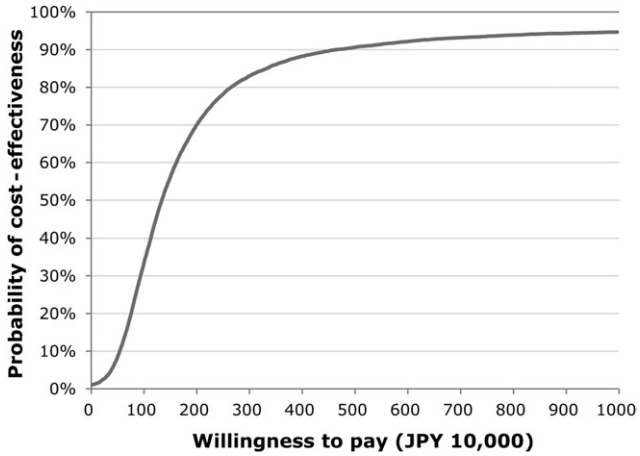

Fig. 4 – Acceptability curve. JPY, Japanese yen.

Simple cost cutting may hinder the development of innovative technologies, but economic evaluation can help clarify the relationship between value and costs of various therapies to determine appropriate treatment strategies. We conclude that adjuvant FOLFOX is cost-effective in Japan for stage III colon cancer compared with FU/LV. Even when more conservative values are used for parameters regarding the benefits of adjuvant FOLFOX, this conclusion does not change. Adjuvant FOLFOX therapy should be considered as a treatment option if oncologists believe that the clinical benefits outweigh the more severe AEs compared with the FU/LV regimen.

Acknowledgment

Source of financial support: This study was funded by the Comprehensive Support Project for Oncology Research (CSPOR) and the Comprehensive Support Project for Health Outcomes Research (CSP-HOR) of the Public Health Research Foundation. The corporate and individual sponsors of this study are listed on the CSPOR Web site (http://www.csp.or.jp/contribution_en.+php). The pharmaceutical manufacturer/distributor who provided financial contribution as a corporate sponsor took no part in this study other than providing information relevant to proper use of the study drugs. All decisions concerning the planning, implementation, and publication of this study were made by the coauthors.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at doi:10.1016/j.jval.2011.10.006 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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